UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SUZANNE DE LA MONTE and JACK R. WANDS

Appeal No. 2006-0299[1]
Application No. 09/964,412

HEARD: March 9, 2006

Before SCHEINER, GRIMES and GREEN, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves a method of treating dementia by administering an antisense oligonucleotide complementary to AD7c-NTP, a neural thread protein said to be expressed at high levels in the brains of Alzheimer's disease patients. The examiner has rejected the claims as lacking enablement. We have jurisdiction under 35 U.S.C. § 134. We will reverse this rejection.

BACKGROUND

Alzheimer's disease "is the most prevalent neurodegenerative disease and the most common cause of dementia in the Western hemisphere."

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[1] This appeal is related to an appeal in application serial no. 09/964,667 (appeal no. 2006-0275). We have considered the two appeals together.

Specification, pages 1-2. "AD neurodegeneration is characterized by prominent atrophy of corticolimbic structures with neuronal loss, neurofibrillary tangle formation, aberrant proliferation of neurites, senile plaques, and βA4-amyloid deposition in the brain." Id., page 2.

AD7c-NTP cDNA was isolated from a cDNA library prepared from the temporal lobe of an individual with end-stage Alzheimer's disease. Specification, page 33. According to appellants, the 1442-nucleotide AD7c-NTP cDNA "is an Alu sequence-containing gene" and "encodes a ~41 kD membrane spanning protein" (id., page 17). AD7c-NTP is expressed in normal brain tissue, but "[q]uantitation of data obtained from 17 AD and 11 age-matched control brains demonstrated significantly higher levels of AD7c-NTP gene expression in AD. In situ hybridization and immunostaining studies localized AD7c-NTP gene expression in neurons, and confirmed the over-expression associated with AD neurodegeneration . . . [These] results suggest that . . . abnormal expression of AD7c-NTP is a phenotype associated with Alzheimer's disease." Id., page 18.

In addition, various neuronal cell lines were stably transfected with AD7c-NTP cDNA and examined for growth properties, morphology, and expression of AD7c-NTP. Specification, pages 45 and 46. "Over-expression of AD7c-NTP . . . resulted in significantly lower densities of viable cells in the cultures, despite normal or elevated levels of DNA synthesis" (id., page 46). The "[r]educed cell density in the cultures was caused by increased cell death" (id.), as shown by the invariable presence of "numerous round, refractile floating [dead] cells" (id.). According to appellants, "[t]he attendant increase in nuclear p53 expression in

AD7c-NTP transfected cells suggests that the cell death is likely to be mediated by apoptosis." Id. Finally, viable cells in the AD7c-NTP transfected cultures exhibited "extensive neuritic growth with fine interconnecting processes [ ] on most cells" and "[i]mmunocytochemical staining . . . using [an] [anti-AD7c-NTP] monoclonal antibody revealed intense labeling of the cell bodies and cell processes" (id.).

According to appellants, "[t]hese studies demonstrate that over expression of AD7c-NTP in transfected neuronal cells promotes neuritic sprouting and cell death, two of the major features of Alzheimer's disease neurodegeneration." Specification, page 46. Thus, reducing AD7c-NTP expression "might be effective in . . . treating or preventing the onset of Alzheimer's disease" (id., page 46).

DISCUSSION

Claims 35 and 37-42, the only claims remaining in the application, are directed to treating dementia by administering an antisense oligonucleotide to inhibit translation of AD7c-NTP mRNA. Claims 35, 37 and 38 are representative:

35. A method for the treatment of dementias of the Alzheimer's type of neuronal degeneration, said method comprising administering to an animal in need thereof an antisense oligonucleotide which is complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1.

37. The method of claim 35, wherein said antisense oligonucleotide is a 15 to 40 mer.

38. The method of claim 35, wherein said antisense oligonucleotide is selected from the group consisting of SEQ ID NO:9, SEQ ID NO:10 AND SEQ ID NO:11.

SEQ ID NO:1 represents the AD7c-NTP cDNA; SEQ ID NOS: 9, 10 and 11 represent portions of SEQ ID NO:1.

All of the pending claims stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The examiner acknowledges that "the specification shows that the recombinant over-expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration" (Answer, page 4). However, the examiner notes that the specification "does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal . . . via the administration of antisense based nucleic acid compounds" (id., page 6), even though "[t]he art of nucleic acid based therapies [is] [ ] unpredictable" (id.).

"When rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The examiner cites a number of references as evidence of "the unpredictability and the problems faced in the antisense art" (Answer, page 7). The problems or challenges enumerated by the examiner are essentially these: identification of an appropriate target in the disease process; identification of an antisense molecule that can interfere with the disease process through specific recognition and affinity; delivery of antisense oligonucleotides to the brain; the

complexity of cellular uptake of antisense oligonucleotides; physical barriers due to internal structures of target RNAs and associations with cellular proteins; and so-called non-antisense effects. Id., pages 6-8.

In addition, the examiner cites a number of references in support of his assertion that the consensus in the art is that many "challenges [ ] remain before the use of antisense becomes routine in a therapeutic setting" (id., page 9), and that antisense therapy is still a long way from "effective and efficient clinical translation" (id.).

Finally, the examiner appears to concede that "the type of experimentation required to practice the invention" is of a "more or less standard nature" (id., page 11), but argues that "the type of experimentation . . . is outweighed by the sheer quantity of experimentation . . . , the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which experimentation should proceed" (id.). The examiner concludes that making and delivering an antisense compound "such that one would be able to treat dementias of Alzheimer's [disease] . . . [would require] undue trial and error experimentation" (id., page 6), given the lack of specific guidance in the specification.

"Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.

Cir. 1988).[2] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis original). In any case, as explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

> [T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point [ ] when it stated:
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> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
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> Ex parte Jackson, 217 USPQ 804, 807 (1982).

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[2] Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the evidence of record shows that, at the time of the invention, those of skill in the art recognized that considerable experimentation would be needed before antisense therapy would be ready for broad clinical application. Nevertheless, that showing alone is not enough to establish that those skilled in the art of antisense therapy would have considered the experimentation required to practice the claimed invention to be undue - what is considered undue is relative, it varies from one field to another. See, e.g., Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (factors relating to undue experimentation include quantity of experimentation necessary, nature of the invention, and relative skill of those in the art).

In this case, the examiner focuses on sources of "unpredictability and [ ] problems [ ] in the antisense art" in general (Answer, page 7), rather than the claimed method in particular. As discussed above, the examiner acknowledges that "the specification shows that recombinant over-expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration" (id., page 4), and does not appear to question appellants' identification of AD7c-NTP as an appropriate target in the disease process. Rather, the examiner's concerns stem from the "unpredictability of the art generally" and the "sheer quantity of experimentation" required to practice the claimed invention, even though the nature of that experimentation is conceded to be "more or less standard" (id., page 11) in the field of antisense therapy.

In our view, the evidence of record establishes that a considerable amount of experimentation and unpredictability was considered to be acceptable in the field of antisense therapy at the time of the invention. Much of the evidence cited by the examiner shows that several clinical trials of antisense drugs had been approved or were ongoing at the time of the invention, despite a widespread recognition in the art that the effects of administering oligonucleotides in vivo were highly variable and complex, and the clinical results generally modest. For example, the examiner cites Jen[3] as evidence of "the challenges that remain before the use of antisense becomes routine in a therapeutic setting" (Answer, page 9), but it is notable that Jen also provides evidence of the approval of "a number of phase I/II trials employing oligonucleotides" (Jen, page 315), despite the fact that "virtually all have been characterized by a lack of toxicity but only modest clinical effects" (id.). Similarly, Agrawal[4] describes several Phase I, II and III clinical trials involving first-generation antisense oligonucleotides (Agrawal, Table 1), while at the same time recognizing the need for "the development of second-generation oligonucleotides, [to] provide improved safety and efficacy" (id., page 386), i.e., to provide improved biological, pharmacokinetic and pharmacodynamic properties (id., page 378, Box 1).

In our view, the approval of multiple clinical trials involving antisense oligonucleotides prior to and at the time of the invention provides evidence that

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[3] Jen et al., "Suppression of Gene Expression by Targeted Disruption of Messenger RNA: Available Options and Current Strategy," Stem Cells, Vol. 18, pp. 307-319 (2000).

[4] Agrawal, "Antisense Oligonucleotides: Towards Clinical Trials," Tibtech, Vol. 14, pp. 376-387 (October 1996).

those of skill in the art would not have considered the problems cited by the examiner to be a source of undue experimentation in this particular field. Moreover, it is well settled that a therapeutic method need not be ready for broad clinical application in order to be enabled. See In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995): "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans."[5]

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[5] The Brana court wrote in terms of of "usefulness," but the rejection on appeal was based on 35 U.S.C. § 112, first paragraph. See 51 F.3d at 1564, 34 USPQ2d at 1439.

In our view, the examiner has not established that the claimed methods would have required experimentation beyond that considered routine in the field of antisense therapy. Thus, we conclude that the examiner has not shown that the amount of experimentation required to practice the claimed invention would have been considered undue by those skilled in the art of antisense methods. The rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement is reversed.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge)
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)
Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Lora M. Green) INTERFERENCES
Administrative Patent Judge)

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